VOL. IX, No. 4 APRIL, 1948

610.5
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MAY 18 1948

BORDEN'S REVIEW *of* NUTRITION RESEARCH

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BORDEN'S REVIEW
of
NUTRITION RESEARCH

Reviews and summaries of research information concerning nutrition and foods. Published monthly, except July and August, by THE BORDEN COMPANY; officers of the Company: Theodore G. Montague, president; E. L. Noetzel, treasurer; T. D. Waibel, secretary. Editorial office: 350 Madison Avenue, New York 17, N. Y.

THE ESSENTIAL FATTY ACIDS

By RUTH WOODS

The essential unsaturated fatty acids, historically though erroneously termed "vitamin F," comprise three acids which have been found to be necessary for life and health in the animal organism. These are linoleic acid, linolenic acid and arachidonic acid. They apparently cannot be synthesized by the animal body as has been demonstrated both by biological and isotopic techniques. When they are absent from the diet a characteristic deficiency disease occurs in experimental animals, the chief feature of which is a scaly dermatitis. If untreated, the deficiency ends fatally. In human beings, particularly in infants, lack of a sufficient supply (probably most likely as a result of faulty utilization) is believed to be associated with the development of eczema. Aside from their vitamin-like activity, these acids are very important from a dietetic point of view because of their high susceptibility to rancidity through exposure to the air. The products of their rancidity may exert a deleterious effect upon the rest of the diet by stimulating oxidative destruction of such factors as vitamin A and vitamin E. On the other hand, fats which have been highly hydrogenated (saturated) to prevent rancidity may have these essential unsaturated acids destroyed in the process and so may be a poor source of these vital factors. Maintaining the keeping quality of unsaturated fats and oils, therefore, is an important problem in maintaining the full nutritional quality of the products with which they may be associated or combined.

A New Deficiency Disease:

The discovery of the vital nature of certain unsaturated fatty acids came about indirectly as a result of studies on the nutritional significance of fat. Although Osborne and Mendel (1) investigated this question as early as 1920, it was not possible at that time to prepare nutritionally adequate synthetic diets sufficiently low in fat. Consequently the necessity for fat in the diet could not be demonstrated. In 1929, however, Burr and Burr (2) described a new diet of high purity which was extremely low in fat. The diet contained highly purified casein, sugar, yeast* and mineral salts. The yeast was de-fatted by extraction with ether. Vitamins A and D were

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*Since the anti-beriberi factor and the pellagra-preventive factor were the only B vitamins then known and since even these were not yet identified (as thiamine and nicotinic acid, respectively) or isolated in purified form, it was necessary to use a natural material, such as yeast, as a source of essential, but unknown B complex factors. Inasmuch as all members of the B complex are water soluble, ether extraction of the yeast in no way affected its nutritive value with respect to these vitamins.

furnished by the highly concentrated, non-saponifiable matter from cod liver oil, only two drops per day being required to supply the animals' needs.

Animals on this diet developed symptoms of a hitherto undescribed nature within two to three months. These began with a generalized scaliness of the skin, progressive scaling and ridging of the tail, followed by actual death of the tissue and loss of part of this organ. Other symptoms included swelling and soreness of the feet, loss of hair, skin sores and hemorrhagic spots. Degeneration of the kidney allowing passage of blood into the urine was a prominent complication and the immediate cause of death.

Additional amounts of vitamins A and D or of the B complex failed to relieve the symptoms. However, as little as 10 drops, or even less, of lard per day effected complete cures. Animals in dying condition responded immediately with improved metabolism and growth. These emaciated animals gained weight rapidly, recovered the smoothness of their skin and tails and were completely normal at the end of ten weeks.

The Curative Factor(s): Comparison of the effect of various fats and oils and analysis of their fatty acid composition soon led to the realization that only the *unsaturated* fatty acids were responsible for the curative effects (3). Further examination of the composition of the curative oils revealed that the essential unsaturated fatty acid was *linoleic acid.* The possibility that other unsaturated fatty acids such as linolenic and arachidonic acids possessed similar therapeutic activity was further indicated.

Two years later, Burr, Burr and Miller (4) confirmed these observations and added linolenic acid to the group of essential unsaturated acids. Although oleic acid is a common unsaturated fatty acid, it was found to be without effect in curing the deficiency syndrome. This substantiated the suggestion that although it is possible for animals on a fat-free diet to synthesize large amounts of fat from dietary carbohydrate, they nevertheless will still suffer from a fat deficiency because they can synthesize only the saturated fatty acids and one unsaturated fatty acid, namely oleic acid. The animals are completely dependent upon the food supply for adequate amounts of linoleic and linolenic acids.

Some years later, Turpeinen (5) reported arachidonic acid (in the form of methyl arachidonate) to be three times as potent in producing weight gains as linoleic acid (in the form of methyl linolate). Turpeinen suggested that the primary need of the body was for arachidonic acid.

During 1938-1939, various groups of investigators confirmed the views that linoleic, linolenic and arachidonic acids were essential for life and for the prevention of a specific deficiency syndrome (5, 6, 7, 8).

Fig. 1. THE ESSENTIAL UNSATURATED FATTY ACIDS

Linoleic Acid— $CH_3\ (CH_2)_3\ (CH_2CH{:}CH)_2\ (CH_2)_7COOH$

Linolenic Acid— $CH_3\ (CH_2CH{:}CH)_3(CH_2)_7COOH$

Arachidonic Acid— $CH_3\ (CH_2)_3(CH_2CH{:}CH)_4(CH_2)_3COOH$

Relative Activity of Various Unsaturated Fatty Acids:

There is considerable difference of opinion as to the relative activity of the various unsaturated fatty acids. At least two factors are responsible: (1) Variations in experimental conditions among different investigators and (2) the multiplicity of physiological responses elicited by the various fatty acids.

Physiological Responses to Essential Unsaturated Fatty Acids: Lack of the essential unsaturated fatty acids evokes a number of deficiency symptoms. Some of these have already been described: Skin and hair symptoms, growth response; derangement of kidney function. In addition, disturbances of fat and water metabolism have been found to be quite common (2, 3, 7, 9, 10, 11, 12) and also disturbances in the reproductive system. These include, in the female, decreased rate of ovulation (2, 5), abnormally prolonged gestation and occasional resorption of the embryo (13), prolonged labor and excessive hemorrhage (14), poor lactation (13). The litters are undersized and often so weak that they soon die. Males show a loss of normal sexual responses and will seldom mate; if they do, they are unable to sire litters (2). Evans (15) has shown that this sterility, which differs from vitamin E deficiency sterility, can be cured by administration of the essential fatty acids.

The three fatty acids (linoleic, linolenic and arachidonic) vary in their activity depending upon which physiological response is being tested. For example, Hume *et al* (16) report both linoleic and arachidonic to be equally effective in curing skin symptoms; Turpeinen (5) has stated that arachidonic is three times as potent as linoleic when measuring growth response; Hume (16) has found it to be only twice as potent as linoleic acid in growth stimulation and has added, further, that linoleic acid is about six times as potent as linolenic for growth (6).

The fatty acids differ not only in their quantitative effects, but also in the qualitative nature of their behavior. For example, not all of those which produce growth will also clear the skin; but all of those effective in clearing the skin will stimulate growth. This differential effect was first noticed with cod liver oil which brought about renewed growth *(not on the basis of its*

vitamin content) without commensurate healing of the scaly skin (17, 18). Table 1 shows these differential effects:

Table 1. CURATIVE EFFECTS OF FATTY ACIDS (19)

Acid	Growth Effect	Skin Effect	Water Consumption
Linoleic	+	+	Normal
Arachidonic	+	+	Normal
Linolenic	+	—	High
Linusic	+	—	
Docosahexenoic	+	—	
Esters of cod liver oil	+	—	High

As Burr (19) points out, however, the differences in this table are not absolute. If, for example, high doses of linolenic acid are fed daily some improvement of the scaly skin condition is obtained (20).

With respect to the growth promoting activities of the various acids, Burr (19) has rated them as follows: Arachidonic, linoleic, linolenic, docosahexenoic and the higher esters of cod liver oil. With respect to their curative effects on skin, the acids are generally graded: Linoleic, most active; arachidonic, intermediate; linolenic, etc., least effective.

Vitamin Interrelationships:

Fat Soluble Vitamins: The ease with which the essential unsaturated fatty acids become rancid makes them an important factor in hastening the rancidity of other dietary factors as well, particularly the easily oxidized fat soluble vitamins A and E. The unsaturated fatty acids have been found to exert antagonistic effects upon carotene and vitamin A. In some instances this has been shown to be due to enzymatic reactions (21); in others, it has not been clear whether the destructive effects were due to inhibition or to actual oxidative destruction of vitamin A by the products of fatty rancidity (22).

B Complex: The essential unsaturated fatty acids have been found to have a close interrelationship with certain members of the vitamin B complex, notably those which are associated with fat metabolism and symptoms

of dermatitis. Most significant of these interrelationships is the pyridoxine supplementing activity of the essential fatty acids. The study of this relationship began in 1935 when Hogan and Richardson (23) indicated that a dermatitis similar to that caused by pyridoxine deficiency could be cured by wheat germ oil. This led Birch and György (24) to find that fat had a strong sparing action on the vitamin. Soon thereafter they showed that fat added to the diet greatly delayed or completely prevented the dermatitis even at time of death. It was concluded that linoleic acid was responsible for the protective action of the fat (in this case, lard) (25). Other workers extended and confirmed these observations (26, 27, 28, 29). The fact that animals on a pyridoxine-deficient diet supplemented with the essential fatty acids often develop a characteristic convulsive syndrome and, in most cases, eventually succumb indicates that the pyridoxine sparing action of these acids is restricted solely to the dermatitis symptoms. The fatty acids, in fact, do not even replace pyridoxine in this respect, but merely delay the onset of symptoms (30, 31, 32).

The fats have a sparing action on thiamine and, if present in large amounts in the diet, increase the requirement for riboflavin (33). This action, however, is believed to be a general one, not related specifically to the activity of the essential fatty acids. A possible relation between these acids and biotin has been suggested by the finding that when corn oil (a source of unsaturated acids) replaces Crisco (a hydrogenated fat) the dermatitis caused by raw egg white (*avidin,* the "anti-biotin" material) is greatly diminished (34).

The interrelationship between the essential fatty acids and the B vitamins associated with various forms of dermatitis and fat metabolism suggests a future possible finding with regard to similar interactions with inositol. Inositol, it will be recalled,* is one of the newer members of the vitamin B complex and is intimately involved in fat metabolism, skin disease symptoms in experimental animals and possibly psoriasis in human beings.

Requirements of Various Animal Species:

Rats: No absolute values are available for the optimum daily intake of linoleic acid. Highest values reported are 100 mg. of linoleic acid per day (or 33 mg. of arachidonic) for maximum *curative* growth response (5). Other workers have reported similar curative responses with the following daily doses of linoleic acid: 60 mg. (3), 20 mg. (35), 42 mg. (6, 16), 40 mg. (20). The extensive studies of Martin (35) with linoleic acid indicate that 20 mg. per day is probably the nearest figure for adequate curative

*cf. *Borden's Review of Nutrition Research,* January and February, 1948, "The Story of Inositol I. and II."

dosage. When fed as a *prophylactic* dose throughout the growth period of young rats, 20 mg. of linoleic acid is also generally considered adequate for producing a normal animal.

Cattle: It has been reported that cows require about 4 per cent or more of fat in the grain ration for optimum milk and fat secretion (36, 37), but as yet this has not been tied in with the essential fatty acid content of the fat. Similarly, young calves do not thrive on a low fat diet (38), but whether this reflects a deficiency of essential fatty acids remains to be shown.

Poultry: Limited studies with chicks indicate, as in cattle, a general dietary requirement for fat which has not been conclusively related to the fatty acids (39).

Swine: The feeding of low fat diets to hogs has been reported to bring about a striking reduction in the linoleic acid content of the lard (40, 41, 42, 43), but no discernible evidence of deficiency symptoms.

Dogs: Recent experiments with dogs (44) show that puppies reared on a low fat diet develop scaly skin which is curable with lard (a source of linoleic acid) or other fats. The susceptibility of dogs to eczema is believed to be another indication of their requirement for linoleic or other unsaturated fatty acids.

Influence of Diet: The quantitative requirements for the unsaturated fatty acids vary considerably, depending upon the composition of the diet. If the carbohydrate is replaced by a fat free from linoleic acid, the growth of the rat is greatly retarded and death soon follows (45, 46). The animals are cured either by feeding linoleic acid or by being changed back to a high carbohydrate diet. Sinclair (46) has reported the need for a higher curative dose of linoleic acid on a high fat diet. This has been interpreted as indicating that the requirement for linoleic acid is greater with high fat diets or else that some synthesis of linoleic acid takes place on high carbohydrate diets. This latter hypothesis has been shown to be improbable in view of the isotope studies of Schoenheimer (47). He found no sign of deuterium "tracers" in the linoleic or linolenic acids of the body tissues indicating that these acids must have been derived directly from the diet and not by body synthesis.

Distribution in Foods:

Large amounts of linoleic and linolenic acids are found in most vegetable and seed fats, except those which are highly hydrogenated. Practically

no arachidonic acid is found in vegetable fats. Fish oils, though rich in unsaturated acids, apparently do not contain the essential ones, except for one of the higher unsaturated acids in cod liver oil which has been shown to bring about a growth response. Animal fats, depending upon the animal's feed, may be fairly rich in all three of the essential unsaturated fatty acids.

Table 2.
ESSENTIAL FATTY ACID CONTENT OF VARIOUS FOODS (48)

Food	*Per Cent*	*Food*	*Per Cent*
Animal Products		*Vegetable Fats*	
Butter	1.9 — 4.0	Barley germ oil	63.0
Beef fat	1.1 — 5.0	Cocoa butter	2.0
Lard	5.0 —11.1	Coconut oil	6.0— 9.2
Mutton fat	3.0 — 5.0	Corn salad oil	70.0
Liver fat	3.0 — 7.0	Cotton seed oil	35.0—50.0
Milk (cow)	0.15— 0.23	Ground nut oil	13.0—27.0
(ewe)	0.36	Linseed oil	72.0—83.0
(goat)	0.22	Maize germ oil	42.0
(human)	0.39— 0.40	Oat germ oil	31.0
(mare)	0.69	Olive oil	4.0—13.7
		Peanut Oil	20.0—24.0
Fish Oils	traces	Rice bran oil	29.0—42.0
		Rye germ oil	48.0
Margarine	2.0 — 5.0	Soy bean oil	56.0—63.0
		Sunflower seed oil	52.0—64.0
		Wheat germ oil	44.0—52.0

In considering the essential fatty acid content of foods, it is important to remember that these compounds easily become rancid upon exposure to air. This means that the essential fatty acids become lost nutritionally. Moreover, the products of such oxidative rancidity may have toxic effects and may further deplete the value of the diet by oxidative destruction of other constituents, notably carotene, vitamins A and E and certain members of the vitamin B complex.

Role of Essential Fatty Acids in Human Nutrition:

Like some of the newer vitamins, the role of the essential fatty acids in human nutrition has not yet been clearly defined. As early as 1919, Von Gröer (49) reported studies on two infants maintained for several months on a diet extremely low in fat. Growth was fairly good, but one child developed a generalized eczema. More than 15 years later, Holt *et al* (50) reported similar studies with a group of three infants, one of whom developed eczema.

These studies led to an experiment with one adult human subject (51). The subject voluntarily subsisted on an almost fat-free diet for six months.

Although this diet produced deficiency symptoms in rats, no ill effects were noted in the human subject. There were, however, certain expected changes such as loss of weight, change in respiratory quotient and a marked drop in the blood levels of linoleic and arachidonic acids. An interesting, unexpected result was a permanent cure of frequent attacks of migraine headaches from which the subject had previously suffered. When it is remembered that even rats do not show marked deficiency symptoms until they have been on the deficient diet for about three or more months it is understandable why such symptoms did not appear in the human subject.

Therapeutic Uses of Essential Fatty Acids: During the course of studies on scaly dermatitis in rats, it was observed that the disease was accompanied by a detectable decrease in the lipids of the blood serum (indicated by a low iodine number) (52). This led to similar studies on human subjects suffering from eczema (53, 54). A distinctly lower content of arachidonic and of linoleic acid was found in the blood lipids of eczematous persons (55). The iodine number was usually lower than normal and in infants with uncomplicated eczema the average difference was found to be about 25 per cent. For example, Hansen (55) found that the average iodine number of the serum fatty acids of eleven infants with eczema was 82, while in eleven normal controls it was 114. When the eczematous infants were given linseed oil, corn oil or soy oil (sources of the essential unsaturated fatty acids), they all improved. Clinical improvement apparently coincided with the rise in the iodine number of the serum.

Other workers reported similar favorable results. Cornbleet (56) treated 87 patients with allergic eczema with four tablespoons of corn oil three times a day. Most of these were adolescents or young adults who had suffered from this condition for many years. Cures were effected in from 12 to 18 months and frequently followed a somewhat erratic course. Faber and Roberts (57) confirmed the low iodine number in the serum lipids of infants with eczema, but could not confirm the curative properties of the unsaturated oils. Failure to improve eczema was reported by Taub and Zakon (58) and by Ginsberg *et al* (59). The latter group also found no difference in the serum lipid iodine number between normal patients and those with eczema.

These contradictory findings may be at least partly explained by the work of Finnerud and associates (60) who found that only 50 per cent of patients with eczema have subnormal blood lipid iodine numbers. In their studies and in all of the cases thus far studied it has been found that usually those patients with eczema who also have a low iodine number respond to therapy with unsaturated oils, while eczematous patients who

have normal or nearly normal iodine values, respond less readily, if at all. In responsive patients, with the clearing of the skin, there is a rise in lipid iodine numbers accompanied by a rise in linoleic acid but not in arachidonic acid. The level of the latter apparently was never low, even when the iodine number was low.

The therapeutic value of the unsaturated fatty acids in certain types of childhood eczema associated with allergy has received more recent confirmation as a result of studies at Minneapolis General Hospital and at the University of Minnesota Medical School. During the course of routine therapeutic procedures at the allergy clinics (including external dermatological therapy, avoiding wool and silk irritants, special elimination diets) it was decided to use a newly available milk substitute product made entirely from vegetable materials (61). This product consisted of a thoroughly homogenized emulsion in which soy bean proteins and other solids were held in suspension with soy bean oil. Results were sufficiently encouraging to stimulate further studies with soy bean products. The evidence of these studies combined with the data reported by Hansen and others on the response of eczema (as correlated with the iodine numbers of blood lipids) to therapy with linseed oil, lard or corn oil, led to similar studies on soy products. The influence of soy oil or of the soybean milk food, containing about 4 per cent of soy oil, on the iodine number of the plasma lipids and on the course of eczema was recently reported by Stoesser (62) in a continuation of the Minnesota studies. He found that infants with severe skin changes exhibited markedly low blood iodine numbers, averaging about 71. These values rose, after three or more weeks of soybean milk therapy, to normal averages of about 118. The increase in iodine number was associated with a definite favorable response of the eczema to external therapy. Increase in iodine number and response to other therapy were not consistently observed, however, in cases of eczema with moderate, widespread skin manifestations.

At present, evidence seems to be accumulating definitely in favor of the view that many eczemas are specifically related to a deficiency of the unsaturated fatty acids—linoleic, linolenic and, possibly, arachidonic—either because of a low intake or because of an abnormally high requirement in certain individuals.

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